American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:107–116 (1996)

Assessing Risk for the Tourette Spectrum of Disorders Among First-Degree Relatives of Probands With Tourette Syndrome

Susan L. Santangelo, David L. Pauls, Philip W. Lavori, Jill M. Goldstein, Stephen V. Faraone, and Ming T. Tsuang

Department of Epidemiology, Harvard Program in Psychiatric Epidemiology and Biostatistics, Harvard School of Public Health (S.L.S., M.T.T.), Department of Psychiatry, Harvard Medical School (J.M.G., S.V.F., M.T.T.), Department of Psychiatry, Tufts New England Medical Center (S.L.S.), Boston, Massachusetts, Child Study Center, Yale School of Medicine (D.L.P.), New Haven, Connecticut, and V.A. Cooperative Studies Coordinating Center, 151K, Department of Veterans Affairs Medical Center, and Stanford University (P.W.L.), Palo Alto, California

Previous studies have indicated that genetic investigations of Tourette syndrome (TS) should focus on a phenotype that includes not only TS, but chronic tics (CT) and obsessive-compulsive disorder (OCD) as well. These studies have shown that sex may play a role in determining which of the disorders in the TS spectrum is expressed in a susceptible individual. Female relatives of TS probands far more often express OCD, while male relatives more often express TS or CT. Data from the Yale Family Study of TS were used to model risk to first-degree relatives of probands with TS for a variety of TS disease phenotypes. Risk to relatives was modeled using multivariate Cox regression analysis, a method appropriate for assessing risk when there is correlation among disease onsets. This is the first known application of this method to family data. The study identified two proband characteristics that increase the risk for disease onset among both male and female relatives for all TS spectrum disorders, lending credence to the hypothesis that TS spectrum disorders share a common etiology. These were a relatively younger age-at-onset, and no experience of simple motor tics. The predictive ability of two additional factors varied by both sex and disease phenotype. These characteristics, i.e., proband onset with compulsive tics, and proband onset with rage, appear to increase risk primarily in female relatives, and for the OCD part of the spectrum.

KEY WORDS: obsessive-compulsive disorder, chronic tic disorder, sex, multivariate Cox regression analysis

INTRODUCTION

Gilles de la Tourette Syndrome (TS) is a neuropsychiatric disorder with onset in childhood and a chronic and lifelong course, characterized by a combination of involuntary motor and vocal tics which wax and wane in number and severity throughout the course. Although its etiology is still unknown, it is believed to have a strong genetic component, and appears to be transmitted in a simple Mendelian fashion. TS displays two characteristics which are hallmarks of Mendelian disorders [Risch, 1994]. It is rare, with population prevalence at about 4–5 per 10,000 [Apter et al., 1993], and the risk to first-degree relatives is extremely high, on the order of 10% [Pauls et al., 1991], or about 200 times the general population prevalence. Although there is some disagreement about the specific mode of transmission, all published reports of genetic analyses of TS pedigrees report typical Mendelian segregation ratios [Baron et al., 1981; Kidd and Pauls, 1982; Comings et al., 1984; Devor, 1984; Price et al., 1984; Pauls and Leckman, 1986; Pauls et al., 1990].

As a result of the Yale Family Study of TS [Pauls et al., 1984, 1986, 1991; Pauls and Leckman, 1986], it is now commonly accepted that the phenotype is broader than TS alone, and includes chronic tics (CT) and obsessive-compulsive disorder (OCD). Reports of increased rates of obsessive-compulsive symptoms in TS patients have existed for more than 20 years [Nee et al., 1980; Fernando, 1967; Morphew and Sim, 1969; Yaryura-Tobias et al.,

Received for publication April 26, 1995; accepted October 3, 1995.

Address reprint requests to Susan L. Santangelo, Sc.D., Department of Psychiatry, New England Medical Center, 750 Washington St., Box 1007, Boston, MA 02111.

1981; Jagger et al., 1982; Montgomery et al., 1982; Frankel et al., 1986], and for an even longer period of time CT has been considered a milder manifestation of TS [Gilles de la Tourette, 1982; Eldridge et al., 1977; Shapiro et al., 1978; Kidd et al., 1980; Nee et al., 1980; Pauls et al., 1981]. However, more recent, persuasive evidence supports the hypothesis that these disorders are various manifestations of a TS spectrum disorder that is transmitted as a single major locus [Pauls et al., 1984, 1986, 1991; Frankel et al., 1986; Pauls and Leckman, 1986; Pitman et al., 1987; Walkup et al., 1988].

The Yale Family Study revealed that there was a sex difference in the frequency of TS spectrum disorders expressed by relatives. Specifically, male relatives more often exhibited TS and CT, while female relatives far more often exhibited OCD without tics. Compared to male relatives, females were three times more likely to be affected with OCD than with CT, and nine times more likely to have OCD than TS [Santangelo, 1992]. This unexpected sex difference in the frequency of TS, CT, and OCD among family members provided evidence that not only is OCD etiologically related to TS, but that it may be a sex-related alternative expression of the disorder.

It is commonly observed that males are at higher risk than females for TS, with a sex ratio of about 3:1. This same sex ratio was evident as well in the Yale Family Study data for the classical TS part of the spectrum. However, when the entire spectrum (TS, CT, and OCD) was considered, the sex ratio decreased to 1.6:1. Thus, the sex difference, at least in affected family members of TS probands, appears not to be a difference in prevalence of the disorder, per se, but more likely a difference in prevalence of the expressed spectrum variant. This observation suggests that sex may play a role in determining which of the spectrum variants is expressed in a susceptible individual.

Although these findings are intriguing, it is difficult to explain them. Until recently [Santangelo et al., 1994], there had never been a study of sex differences among TS patients, so little was known about how the syndrome manifests in females or how that may differ from manifestation in males. The Yale Family Study had shown that neither proband sex nor proband OCD status predicted which spectrum variant would be expressed in relatives [Pauls et al., 1991; Pauls and Leckman, 1986]; however, the influence of sex as a possible source of phenotypic or genetic heterogeneity of the syndrome has not previously been explored.

In order to properly characterize the phenotype for genetic analyses it will be necessary to be able to discriminate between those disorders which are legitimate alternative expressions of a putative TS gene and those which are not true spectrum disorders, but merely mimic them. Unfortunately, at the present time, there are no empirical (or any other) bases on which to discriminate between cases of CT and OCD that are etiologically related to TS and those that are not.

There is evidence that the common wisdom about the relationship between TS and CT, i.e., that TS and CT arise from the same genetic diathesis, should perhaps be reconsidered. The DSM-III-R criteria for TS [American Psychiatric Association, 1987] require both motor and vocal tics; if only one or the other is present, the diagnosis given is for chronic tics. Chronic tics are much more common than TS. The population prevalence of chronic tic disorder (including both single and multiple chronic tics) has been estimated at 2.7% [Pauls et al., 1991], which is over 50 times the 5/10,000 prevalence estimate for TS. This situation is analogous to the one that results when, for example, investigators of a psychiatric disease like bipolar disorder expand the boundaries of the disorder among family members to include other affective disorders, particularly unipolar depression, and the prevalence estimate explodes. The vast difference in prevalence between CT and TS may be an indication that perhaps not all chronic tics are etiologically related to TS. The chronic tic disorder itself may be etiologically heterogeneous.

Sometimes the CT disorder is prodromal, i.e., a child who onsets with CT may go on to develop full-blown TS. However, there is presently no way to predict who will do that and who will not. Worse, there is currently no way to distinguish between *persistent* chronic tics that are etiologically related to TS and those that are not.

In a similar vein, the population prevalence of OCD (ranging from 1–3% with no significant difference between men and women) [Karno, et al. 1988] is between 20–60 times the prevalence of TS. Approximately one third of TS probands have family members with OCD [Nee et al., 1980; Pauls et al., 1981; Pitman et al., 1987], and rates of OCD without tics among those relatives range from 13–25% [Pauls and Leckman, 1986; Pitman et al., 1987]. The proportion of OCD patients with a positive family history of tics has been estimated to be as high as 50% [Pitman et al., 1987], which means that at least half of OCD probands do *not* have relatives with tics. However, a more recent report [Pauls et al., 1995] found the rate of tics (both TS and CT) among first-degree relatives of probands with OCD to be 4.6%, a significant difference from the rate (1%) in a sample of relatives of normal controls. Therefore, it is possible that OCD, like chronic tics, is etiologically heterogeneous as well, which is, in fact, the conclusion of Pauls [1992] and Pauls et al. [1995]. There is no reason to assume that all OCD cases or all cases of CT in the population at large necessarily belong in the TS spectrum.

The possibility of expanding the boundaries of TS, with its potential for faster, higher-yield data collection, must be weighed against the potential loss in accuracy in model specification and parameter estimation. Expanding the boundaries of the syndrome to include CT and OCD, in a manner analogous to expanding the boundaries of schizophrenia to include all of the schizophrenia spectrum disorders, has the potential to drastically alter the range of plausible genetic models. Further, the failure of several linkage studies to find even a suggestive chromosomal location for TS or the TS spectrum suggests that a reexamination of the phenotype may be warranted.

This report will explore these issues by modeling the risk to first-degree relatives of TS probands for disease phenotypes consisting of different combinations of TS spectrum disorders. The working hypothesis is that the

Tourette spectrum (TS, CT, and OCD) is caused by a single major autosomal-dominant gene whose phenotypic expression is modified by one or more genetic or environmental risk factors. The range of phenotypic expression of a putative TS gene is presumed to be associated with sex and possibly other risk factors.

In order to test the hypothesis, these analyses will address the following questions: are the different disease phenotypes predicted by different risk factors? Do the effects of the risk factors for any given phenotype vary by relative type? What is the relationship between the risk factors which predict the various disease phenotypes and sex (are there interactions)?

MATERIALS AND METHODS

Yale TS Family Study Methodology

Data are from the Yale Family Study of Gilles de la Tourette Syndrome. Sampling and data collection procedures have been described in detail elsewhere [Pauls et al., 1984, 1991; Pauls and Leckman, 1986]. Briefly, probands were randomly selected from the membership of the Connecticut chapter of the Tourette Syndrome Association (TSA) for a large family study of TS. Female members of the TSA were oversampled in order to insure sufficient numbers of female probands and their families for data analyses.

DSM-III-R criteria for TS were determined by direct interview of subjects over age 18 years, and interviews of parents of those under age 18, using adult and child versions of a precoded structured interview instrument developed specifically for this study [Pauls and Hurst, 1981]. The child version of the interview, administered to a parent about his/her child, included the Schedule for Affective Disorders and Schizophrenia for School Age Children [Puig-Antich et al., 1980]. The adult version of the instrument incorporated the Diagnostic Interview Schedule [Robins et al., 1980]. Both versions of the instrument included an expanded OCD section, designed to elicit more detailed information on symptoms of obsessions and compulsions.

Whenever possible, subjects under age 18 years were also observed and interviewed regarding their symptoms of TS and OCD, and medical records pertinent to the diagnosis of TS were obtained. Since data were also collected on control probands and their family members, interviewers were blind to the illness status of the proband when interviewing family members. Diagnosticians were also blind to proband diagnoses when diagnosing family members, and were never allowed to evaluate an entire family at once.

Data were collected on 92 TS probands, 85 of whom were either not adopted or had access to information about their biological first-degree relatives. The sample has been described in detail elsewhere [Pauls et al., 1991; Santangelo et al., 1994]. Seventy-four percent of the probands were male. Thirty-three probands (36%) had a concomitant DSM-III-R diagnosis of OCD.

For this report, the data consisted of 338 individuals from 85 families, all of whom were biological first-degree relatives of TS probands. There were 84 fathers, 85 mothers, 61 brothers, 83 sisters, 13 sons, and 12 daughters. Excluding probands, there were 11 families with 2 members, 30 families with 3 members, 19 families with 4 members, 13 families with 5 members, 7 families with 6 members, 3 families with 7 members, 1 family with 9 members, and 1 family with 13 members. Mean family size, excluding the proband, was 3.98.

Disease Phenotype Definitions in Relatives

The determination of which relatives were affected was made according to three distinct disease phenotypes, with different inclusion and exclusion criteria (see Fig. 1). The most inclusive phenotype, designated TS/CT/OCT, included all of the spectrum disorders: Tourette syndrome, chronic tic disorder, and OCD. Relatives with TS and those with chronic tics may also have OCD (although not necessarily), while those designated as having OCD may or may not have tics. Criteria for TS, CT, and OCD were defined by DSM-III-R. Secondly, phenotype TS/OCD included TS, with or without OCD, and OCD with or without chronic tics. CT unaccompanied by OCD was excluded. Finally, the phenotype designated TS/CT included not only TS, but also chronic tics, with or without concurrent OCD. OCD occurring without tics was excluded. Two additional phenotypes were initially defined, but due to the infrequent occurrence of these phenotypes (TS alone, and either TS or CT in the presence of OCD) among the family members, we were unable to model risk for them.

Proband Characteristics Examined as Potential Risk Factors

A previous descriptive epidemiologic report [Santangelo et al., 1994] identified several proband clinical characteristics which discriminated between proband groups defined by sex or OCD status. Those proband characteristics were explored in these analyses as potential risk factors for various disease phenotypes in relatives. Included were certain tic symptoms which were present at *onset* of the disorder (it was possible to onset with more than one type of tic symptom). Those which were shown to discriminate between male and female probands included compulsive tics, complex motor tics, and a behavioral symptom characterized by sudden and explosive anger, irritability, temper outbursts, and aggression, which will henceforth be referred to as "rage." This symptom was four times more prevalent in males at onset. Complex motor tics consisted of several stereotyped movements, including arm, hand, and finger movements, kicking, hopping, other leg movements, tensing parts of the body, echopraxia, and self-injurious behavior. Some complex tics are difficult to differentiate from compulsions. These tics, which included repetitive touching of objects, one's own or others' body parts, tapping fingers or hands, and the subjective feeling of being unable to begin an action, were grouped together under the heading of compulsive tics. They, along with complex motor tics, were about 2.5 times more prevalent in females at onset.

Any complex tics (motor and vocal), as well as complex motor tics alone, also discriminated between probands with OCD (TS + OCD) and without OCD (TS − OCD). These tic symptoms were 2–3 times more prevalent at onset among TS + OCD probands. Com-

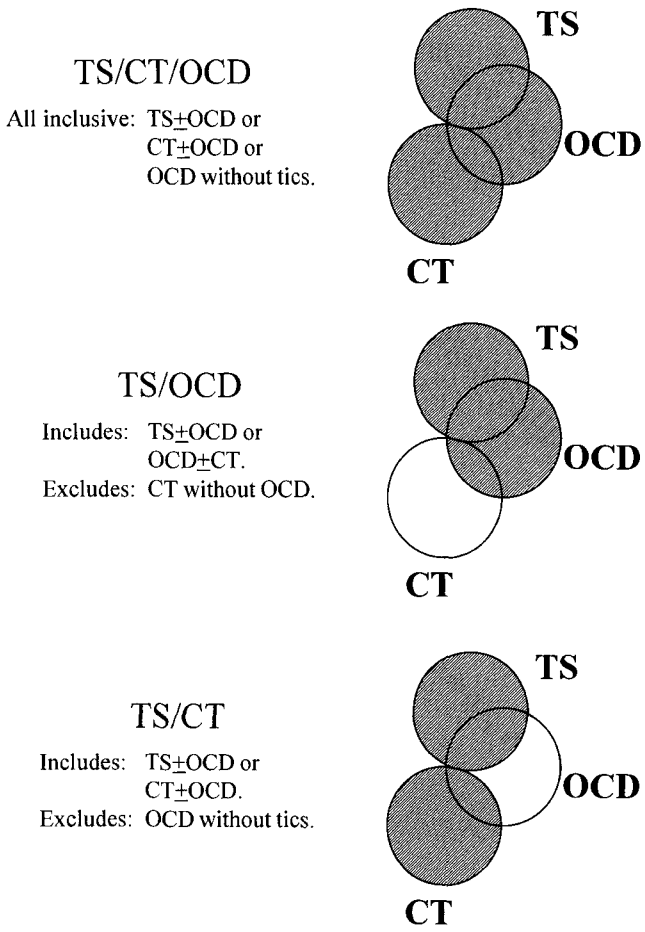

Fig. 1. Phenotype definitions. Shaded portions are included, blank portions are excluded. TS: Tourette Syndrome; OCD: Obsessive Complusive Disorder; and CT: Chronic Tics.

plex vocal tics consisted of involuntary utterance of words, echolalia, and coprolalia.

While rage occurred more often at onset for males, that particular composite of symptoms was reported to occur more frequently among females, and among TS − OCD probands, over the lifetime course of their TS. Simple motor tics occurring at any point in the lifetime course were more prevalent among males and among TS − OCD probands. Any simple tics (motor and vocal) and simple vocal tics alone, occurring at any point in the course, discriminated between male and female probands. Simple motor tics included eye blinking, other facial tics, and head, shoulder, and stomach jerks. Simple vocal tics included grunting, coughing, throat clearing, sniffing, barking, and other noises. Simple vocal tics and any simple tics were more prevalent among males.

Although age at onset did not discriminate between proband groups in this sample, it has been associated with increased risk for other psychiatric disorders. Therefore, proband age at onset, defined as proband age at first tic symptom development, along with proband sex and OCD status, were examined as well. A total of 13 proband characteristics were tested for their potential to predict risk to relatives, including whether or not the proband had any medical problems predisposing to tics prior to or concurrent with development of tics (such as severe head injury, seizure disorders, meningitis, and encephalitis), and whether or not the proband had experienced sensory precursors to tics [Bliss, 1980; Kurlan et al., 1989; Leckman et al., 1993; Santangelo et al., 1994].

Analytic Method

The method chosen to model risk to relatives was the Cox regression analysis of multiple failure time variables. This multivariate method and the computer software, known as MULCOX, were developed to handle multiple failure times with correlated hazards [Wei et al., 1989; Lin and Wei, 1989; Lin, 1990], such as individuals with multiple tumor recurrences or multiple episodes of infection.

This work is the first known application of the method to the analysis of family data. In this situation, the unit of analysis was not the individual but the *family,* and all family members had the potential for failure, or disease onset. Therefore, within each family there existed the potential for multiple failures and the hazards, or probabilities of onsetting, were likely to be correlated among family members. Since it does not account for the correlational structure in the data, the traditional Cox proportional hazards model can overestimate the precision of the regression parameter estimates by underestimating the standard errors of the estimates. The multivariate Cox regression method accounts for the correlated hazards among family members and, thus, provides appropriate estimates of the significance of the regression parameter estimates.

The method itself [Wei et al., 1989; Lin and Wei, 1989; Lin, 1990], and its application to the analysis of data from the Yale Family Study of TS [Santangelo, 1992; Santangelo et al., 1993], have been described elsewhere. Instead of imposing specific structures of dependence among correlated multiple failures, MULCOX models the marginal distribution of each failure time variable with a separate Cox proportional hazards model. For the multivariate inference, MULCOX takes into consideration the correlational structure of the parameter estimators in the marginal failure time models. This technique uses the maximum likelihood method of estimation. Regression parameters (log hazard ratios) are estimated by maximizing the failure-specific partial likelihoods. The parameter estimators across all types of failures (pooled estimators) have been shown to be asymptotically jointly normal, with a covariance matrix that can be estimated from the data. This allows for the evaluation of both the overall performance of a given covariate, as well as how its effects may vary among the failure time variables.

In this application, each type of relative represented a unique type of failure time (the marginal distributions), so that mothers were considered separately from

fathers, first, second, and third siblings, and first and second offspring. The mechanics of the computer program require the sequential ordering of multiple instances of any particular relationship to the proband, such as multiple siblings and offspring. Hence, the typical family consisted of a father (of the proband), mother, oldest brother, next oldest brother . . . , youngest brother, oldest sister, next oldest sister . . . , youngest sister, oldest son, next oldest son . . . , youngest son, oldest daughter, next oldest daughter . . . , youngest daughter. However, any particular family may have had some of these relationship categories "empty" because the corresponding individual either did not exist or was unavailable for assessment. A unique regression coefficient (the log hazard ratio) was estimated for each relative type, corresponding to each covariate.

In this application, model building proceeded by first estimating a series of models containing four relative types (failure times) and two covariates (proband clinical characteristics, described above). Covariates were eliminated from further consideration if the significance level was above .05. Those that were retained, were included together in the same model and tested in the presence of one another, across the relative types.

RESULTS

Tables I–III display the numbers and adjusted proportions of family members affected in each class of relatives, within each disease phenotype. Risk to relatives was modeled for three phenotypes: TS/CT/OCD, TS/OCD, and TS/CT. Rates of illness are for lifetime prevalence, or cumulative incidence, of the disorders and are age-adjusted (when indicated) via survival analysis methods (the LIFETEST procedure in SAS [1990]).

Phenotype TS/CT/OCD

Overall, 76% of all families had at least 1 family member (in addition to the proband) affected with TS/CT/OCD. After adjusting for variable age at onset, 38% (n = 115) of first-degree relatives were affected with this phenotype. Proportions of relatives affected in each class of relationship to the proband are shown in Table I.

Phenotype TS/OCD

Sixty-eight relatives were affected with phenotype TS/OCD, for an age-adjusted rate of 23% (Table II). Fifty-eight percent of families had at least 1 member affected.

Phenotype TS/CT

Eighty-three relatives were affected with TS/CT, for an age-corrected rate of 26% (Table III). Sixty-one percent of all families had at least 1 member affected with this phenotype.

Modeling Risk for Phenotype TS/CT/OCD

Three proband characteristics were found to predict risk to relatives for phenotype TS/CT/OCD. These were the age at which the proband first developed any tic symptoms, the occurrence of simple motor tics at any time during the course of the proband's illness, and the presence in the proband of rage at onset.

TABLE I. Numbers of Relatives and Number Affected in Each Relationship Category for Disease Phenotype TS/CT/OCD: Tourette Syndrome (±OCD), Chronic Tics (±OCD), OCD Alone

Relative types	N	Number ill	Age-adjusted %	
			Males	Females
Fathers	84	37	.44	
Mothers	85	28		.33
Brothers	61	19	.38	
Sisters	83	22		.31
Sons	13	6	.53	
Daughters	12	3		.30
Total	338	115	.44	.33

These three predictors were included in the same model and tested in the presence of one another. Three multivariate hypotheses, corresponding to the three risk factors, were tested. Each tested whether or not the parameter estimates for the corresponding predictor were significantly different across the relative types (failure times). The Wald statistic is a measure of the homogeneity of the coefficients across failure times. It is distributed as a chi-square (with degrees of freedom equal to 1 less than the number of failure times) under the null hypothesis that the effects are the same across the failure times. Except where otherwise indicated, the Wald test for the multivariate hypotheses was nonsignificant, indicating that the estimates were similar, and could be pooled across relative types. Therefore, the common parameters or pooled estimates of effects across the relative types were used (shown in Table IV).

Hazard ratios and approximate confidence intervals were produced by exponentiation of the pooled coefficients and their standard errors. Each of the three covariates (proband age-at-onset, simple motor tics occurring at any time during the course, and rage at onset) remained significant after controlling for the other two.

Although the proband's age at first tic symptom development had not previously discriminated between proband groups on the basis of either sex or OCD status, it did predict risk to relatives. The regression coefficient reported in Table IV is negative (and the hazard ratio below 1) because it corresponds to increasing age in the proband. The risk was *decreased* among relatives of probands who developed their first tic symptoms at

TABLE II. Numbers of Relatives and Number Affected in Each Relationship Category for Disease Phenotype TS/OCD: Tourette Syndrome (±OCD), or OCD (±CT)

Relative types	N	Number ill	Age-adjusted %	
			Males	Females
Fathers	84	17	.20	
Mothers	85	18		.21
Brothers	61	11	.24	
Sisters	83	16		.22
Sons	13	5	.43	
Daughters	12	1		.09
Total	338	68	.24	.22

TABLE III. Numbers of Relatives and Number Affected in Each Relationship Category for Disease Phenotype TS/CT: Tourette Syndrome (±OCD), or Chronic Tics (±OCD)

Relative types	N	Number ill	Age-adjusted % Males	Age-adjusted % Females
Fathers	84	32	.38	
Mothers	85	15		.18
Brothers	61	15	.28	
Sisters	83	12		.15
Sons	13	6	.52	
Daughters	12	3		.30
Total	338	83	.36	.17

relatively *older* ages. In this situation, it is more convenient to consider the inverse of the hazard ratio (1.09), in order to see that the *younger* the proband was at first tic symptom development, the *greater* the risk of becoming ill for the proband's family members. The risk among family members increased by 1.09 for *each year* of decrease in the proband's age at onset.

Simple motor tics were highly prevalent. They were experienced at some point in the course of illness by 66% of probands in this sample. However, the risk of becoming ill was significantly smaller among relatives of probands who had ever experienced this symptom. Again, considering the inverse of the hazard ratio, the risk was 1.77 times *greater* among relatives of probands who had *never* experienced simple motor tics than among relatives of probands who had experienced simple motor tics at some time in the course of their illness.

Finally, for relatives of probands whose symptom picture at onset included rage, the risk of developing any of the TS spectrum disorders was 1.75 times as large as for relatives of probands who had not experienced rage at onset.

Results were essentially the same for each sex when models were estimated separately for male and female relatives. However, stratification by sex revealed a difference in effect size for one factor. The effect of rage at onset in the proband was larger for female than for male relatives (hazard ratio = 2.2 for females, vs. 1.3 for males).

Modeling Risk for Phenotype TS/OCD

Two significant risk factors were identified for this phenotype. Age-at-onset was a significant risk factor for this phenotype, as it was for the previous one. The risk among family members increased by 1.11 for each year of decrease in the proband's age-at-onset. For the relatives of probands who experienced compulsive tics at onset, the risk of developing phenotype TS/OCD was 1.77 times as great as for relatives of probands who did not onset with compulsive tics (Table V).

Although the Wald test indicated that estimates were not significantly different across relative types, the coefficients for each of the covariates were appreciably larger for the female relative classes (mothers and sisters) than for the males. Pooled coefficients were estimated and tested separately for male and female relative types in order to see if there was substantial variation of effect sizes by sex. In fact, the magnitude of effects varied considerably by sex. Although neither covariate was a significant risk factor for male relatives, effects of both covariates were substantially larger, and were significant, for female family members (Table VI). Among mothers and first sisters, the risk increased by 1.18 for each year of decrease in the proband's age-at-onset, and by 2.51 times for presence of compulsive tics at onset in the proband.

Modeling Risk for Phenotype TS/CT

Three covariates were identified as significant risk factors for phenotype TS/CT, the same three that were identified for the first disease phenotype (TS/CT/OCD). For all three risk factors, the pooled coefficients and the exponentiated hazard ratios (Table VII) were quite similar to the estimates for the first, more inclusive disease phenotype (Table IV). For proband age-at-onset and for occurrence of simple motor tics at any time during the course of the proband's illness, the direction and magnitude of the hazard ratios were virtually identical for the two phenotypes. For relatives of probands who experienced rage at onset, the hazard ratio was a bit lower for phenotype TS/CT (1.62, vs. 1.75 for TS/CT/OCD), and the significance level was marginal ($P = .06$).

Performance of Risk Factors Across All Three Phenotypes

In the final stage of data analysis, the aim was to assess whether the risk to relatives varied by phenotype definition. We wanted to evaluate whether or not there were risk factors which were unique to any of the family member disease phenotypes, or if any or all of the identified risk factors performed equally well for all of the phenotypes. A model was estimated in which the failure time variables were the disease phenotypes, and the unit of analysis was the individual (in earlier models, the failure time variables corresponded to the relative types and the unit of analysis was the family). This

TABLE IV. Pooled Parameter Estimates and Their Corresponding Hazard Ratios for Significant Predictors of Risk to Relatives*

Covariate	Pooled β estimate	Z score	*P* value	Hazard ratio	95% confidence interval
Age at onset	−.09 ± .02	−3.66	.0003	0.91	0.88, 0.95
Simple motor tics	−.57 ± .22	−2.63	.009	0.57	0.36, 0.88
Rage at onset	.56 ± .22	2.54	.011	1.75	1.13, 2.72

*Phenotype = TS/CT/OCD: TS (±OCD), CT (±OCD), OCD alone.

TABLE V. Pooled Parameter Estimates and Their Corresponding Hazard Ratios for Significant Predictors of Risk to Relatives*

Covariate	Pooled β estimate	Z score	P value	Hazard ratio	95% confidence interval
Age at onset	−.11 ± .03	−3.13	.002	0.90	0.84, 0.96
Compulsive tics at onset	.57 ± .27	2.16	.031	1.77	1.04, 3.01

*Phenotype = TS/OCD: TS (±OCD), or OCD (±CT).

is the standard use of the method where each individual has the potential for multiple failures. In this case, each individual had the potential to onset with more than one of the disease phenotypes. Although the correlation among multiple onsets within individuals was accounted for in this model, the correlation among family members for the probability of becoming ill was not. Therefore, the precision of the regression coefficients may be overestimated in this model. However, the model was merely being used to provide an approximate test of the variation across phenotypes in the strength of risk factors which had already been identified. Results of testing all of the previously identified risk factors across the three phenotypes are shown in Tables VIII and IX.

Inspection of Table VIII reveals that coefficients were consistent across all three phenotypes for the first two risk factors, i.e., age-at-onset and simple motor tics. For the last factor, compulsive tics at onset, it is apparent that there was considerable variation across phenotypes, despite an insignificant Wald test. Its predictive power seemed to be strongest for the second phenotype (TS/OCD), and weakest for the third (TS/CT). It is apparent that rage at onset was a strong risk factor for the first and third phenotypes, while compulsive tics at onset was a strong risk factor only for the second. In fact, controlling for the other factors, compulsive tics at onset was no longer a significant risk factor when estimates were pooled for all three phenotypes (Table IX).

Covariates which were significant risk factors for all three disease phenotypes, after controlling for the other factors, included age-at-onset and simple motor tics. Although not a particularly strong risk factor, onsetting with rage also appeared to be fairly consistent across phenotypes. Its performance improved when compulsive tics were removed from the model ($\beta = .44 \pm .22$, $P = .05$; hazard ratio = 1.56).

Finally, models corresponding to those shown in Tables VIII and IX were estimated separately for men and women to test for variation across phenotypes by sex. The results are summarized in Table X. The controlled, pooled estimates for age-at-onset and simple motor tics were quite consistent across sex. However, the magnitude of the estimates for the remaining two factors appeared to differ by sex. Across all three phenotypes, both rage at onset, and compulsive tics at onset, appeared to be stronger risk factors for female than for male family members, after controlling for the other factors.

DISCUSSION

Four distinct proband characteristics emerged as significant predictors of risk to first-degree relatives of TS probands for various combinations of TS spectrum disorders. Two of these characteristics (a relatively younger age at first tic symptom development, and no experience of simple motor tics) increased the risk for disease onset among relatives of both sexes and for all three disease phenotypes modeled. The predictive power of the remaining two proband characteristics (onset with rage, and onset with compulsive tics) varied by both sex and disease phenotype.

The existence of risk factors that perform equally well for all three disease phenotypes lends support to the hypothesis that, in these families, the spectrum disorders (TS, CT, and OCD) share a common etiology. It has been documented [Robertson, 1989; Devor, 1990; Singer and Walkup, 1991] that for the majority of patients, the first tic symptoms are simple motor tics, particularly of the face and head, and that these generally appear around age 7 years. For the tics which follow, there is generally a rostral-caudal progression of muscle group involvement that can extend as far as the legs and feet [Devor, 1990; Singer and Walkup, 1991]. Complex motor and vocal tics are typically the last onset tics. One might speculate that onset at a very young age, and exhibiting the more complex tic symptomatology at the very beginning, would be indicators of a particularly severe form of the disorder. If so, then probands with these characteristics may suffer from a

TABLE VI. Pooled Parameter Estimates and Their Corresponding Hazard Ratios for Significant Predictors of Risk to Female Relatives*

Covariate	Pooled β estimate	Z score	P value	Hazard ratio	95% confidence interval
Age at first tics	−.16 ± .05	−3.04	.002	0.85	0.76, 0.95
Compulsive tics at onset	.92 ± .39	2.39	.017	2.51	1.16, 5.44

*Phenotype = TS/OCD: TS (±OCD), or OCD (±CT).

TABLE VII. Pooled Parameter Estimates and Their Corresponding Hazard Ratios for Significant Predictors of Risk to Relatives*

Covariate	Pooled β estimate	Z score	*P* value	Hazard ratio	95% confidence interval
Age at onset	−.07 ± .03	−2.22	.03	0.93	0.88, 0.99
Simple motor tics	−.56 ± .25	−2.24	.03	0.57	0.34, 0.94
Rage at onset	.49 ± .26	1.90	.06	1.62	0.95, 2.70

*Phenotype = TS/CT: TS (±OCD), or CT (±OCD).

particularly virulent genetic defect that is almost always shared with their first-degree relatives.

Two factors were found to predict risk for some but not all of the spectrum disorder combinations. For instance, the occurrence of compulsive tics at onset in the proband was found to be a significant risk factor for disease phenotype TS/OCD, but not for the other two phenotypes. The TS/OCD phenotype excluded chronic tics which occurred in the absence of OCD. Hence, phenotype TS/OCD was the one most heavily weighted with family members who had OCD. Therefore, the predictive power of the factor, compulsive tics at onset, appeared to be greatest for the OCD part of the spectrum. Relatives of probands who onset with compulsive tics may be at higher risk for expressing OCD, than for expressing either TS or CT.

Rage at onset emerged as a significant factor for phenotypes TS/CT/OCD and TS/CT, but not for TS/OCD. The third phenotype, TS/CT, excluded OCD occurring in the absence of tics, so it was more heavily weighted with family members diagnosed with TS and CT. This finding suggests that relatives of probands who onset with rage may be more likely to express TS or CT than OCD without tics. However, the first phenotype included OCD in the absence of tics, so the meaning of this finding is unclear.

However, both factors, proband onset with rage and proband onset with compulsive tics, appeared to be stronger predictors of risk for female than for male family members. Patterns in relationships between risk factors and sex are revealed most clearly in Table X, which summarizes the results of modeling risk for male and female relatives across all three disease phenotypes. These findings are consistent with the results of the sex-specific models within each disease phenotype.

The majority of affected female relatives included in the models had OCD, either alone, or in combination with TS or CT. Sixty-seven percent of mothers and first sisters who were affected with any of the spectrum disorders carried a diagnosis of OCD. Therefore, it is likely that the two risk factors whose effects appear to vary most by sex of the relative are actually risk factors for the OCD part of the spectrum. It is possible that these factors identify a subgroup of relatives, mostly women but including some men, for whom the genetic vulnerability is uniquely expressed as OCD.

It was stated above that Pauls et al. [1991; Pauls and Leckman, 1986] had shown that proband sex did not differentially predict risk to relatives, nor predict which spectrum variant would be expressed in the relative. However, this study may not have been able to adequately test this hypothesis because of the possibility that the female probands in this sample may have been atypical, and more severely affected than the norm: i.e., if TS is the more common expression of genetic vulnerability for males and OCD is the more typical expression in females in general, as it is for the female relatives of TS probands, then women who exhibit full-blown TS, such as the female probands in this sample may represent a unique subgroup of women with the genetic diathesis. By sampling only from probands with TS, this study would have eliminated females with the more common manifestation of the disorder. Therefore, it is possible that the female probands in this study represent a more severe expression of the disorder among females with the TS genetic diathesis. If that is the case, then we cannot conclude from this study that the risk to relatives of male and female probands is the same.

Although results must be considered preliminary until replicated, this study has identified two proband characteristics that appear to increase risk to both male and female relatives, for all TS spectrum dis-

TABLE VIII. Test for Variation in Coefficients for Four Previously Identified Risk Factors Across Three Disease Phenotypes*

Covariate	Phenotypes			Wald statistic	*P* value
	TS/CT/OCD	TS/OCD	TS/CT		
Age at onset	β_{11}, −.07	β_{12}, −.07	β_{13}, −.05	2.82, $df = 2$	.25
Simple motor tics	β_{21}, −.56	β_{22}, −.41	β_{23}, −.61	0.57, $df = 2$	.75
Rage at onset	β_{31}, .43	β_{32}, .25	β_{33}, .44	0.62, $df = 2$	.73
Compulsive tics at onset	β_{41}, .23	β_{42}, .62	β_{43}, .002	4.44, $df = 2$	.11

*β coefficient = natural logarithm of hazard ratio (presence vs. absence of a binary covariate, or per unit change in scale for a continuous covariate) for a given phenotype. First β subscript indicates order of the covariate in the model. Second β subscript indicates phenotype (1, TS/CT/OCD; 2, TS/OCD; 3, TS/CT).

TABLE IX. Parameter Estimates, Pooled Across Three Phenotypes, and Their Corresponding Hazard Ratios for Previously Identified Risk Factors

Covariate	Pooled β estimate	Z score	*P* value	Hazard ratio	95% confidence interval
Age at onset	−.06 ± .03	−2.33	.02	0.94	0.90, 0.99
Simple motor tics	−.53 ± .18	−2.87	.004	0.59	0.41, 0.85
Rage at onset	.39 ± .23	1.66	.10	1.48	0.92, 2.36
Compulsive tics at onset	.27 ± .20	1.37	.17	1.31	0.88, 1.96

TABLE X. Coefficients and Corresponding Hazard Ratios, Pooled Over Three Phenotypes, for Previously Identified Risk Factors Compared for Male and Female Relatives, Modeled Separately

	Male relatives		Female relatives	
Covariate	β estimate	Hazard ratio	β estimate	Hazard ratio
Age at onset	−.06 ± .04	0.94	−.06 ± .04	0.94
Simple motor tics	−.58 ± .24	0.56	−.49 ± .28	0.62
Rage at onset	.12 ± .30	1.12	.65 ± .36	1.92
Compulsive tics at onset	−.05 ± .27	0.95	.57 ± .30	1.77

orders, lending credence to the hypothesis that TS spectrum disorders share a common etiology. Two additional risk factors have also been identified which appear to increase risk primarily in female relatives, and for the OCD part of the spectrum. Exactly what the relationship is between these factors and spectrum OCD remains to be elucidated. However, we are hopeful that identification of these risk factors may provide another in a series of clues which will eventually lead to a description of the etiologic mechanism by which males and females differentially express an underlying genetic susceptibility for the TS spectrum of disorders.

ACKNOWLEDGMENTS

This paper was presented in part at the 1993 World Congress on Psychiatric Genetics, New Orleans, LA, October 2–5, 1993; Dr. Santangelo was recipient of the Junior Investigator Award. We are grateful to Drs. Paul Van Eerdewegh and Susan Folstein for their careful reading and helpful comments on the manuscript, and to John Alsobrook, David Shera, and Meredith Warshaw for technical assistance. This work was supported in part by the National Institute of Mental Health, National Research Service Award MH 17119-10 (a training fellowship to Dr. Santangelo), MH00508 (a Research Scientist Development Award to Dr. Pauls), MH49351, and K21MH00976 (a Scientist Development Award to Dr. Goldstein), and by National Institutes of Health award NS16648.

REFERENCES

American Psychiatric Association (1987): "Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised." Washington, DC: American Psychiatric Association, pp. 75–77, 234–235.

Apter A, Pauls DL, Bleich A, Zohar AH, Kron S, Ratzoni G, Dycian A, Kotler M, Weizman A, Gadot N (1993): An epidemiological study of Gilles de la Tourette's syndrome in Israel. Arch Gen Psychiatry 50:734–738.

Baron M, Shapiro E, Shapiro A, Rainer J (19810: Genetic analysis of Tourette syndrome suggesting major gene effect. Am J Hum Genet 33:767–775.

Bliss J (1980) Sensory experiences in Gilles de la Tourette's syndrome. Arch Gen Psychiatry 37:1343–1347.

Comings D, Comings B, Devor E, Cloninger C (1984): Detection of major gene for Gilles de la Tourette syndrome. Am J Hum Genet 36: 586–600.

Devor E (1984): Complex segregation analysis of Gilles de la Tourette syndrome: Further evidence for a major locus mode of transmission. Am J Hum Genet 36:704–709.

Devor E (1990): Untying the Gordian knot: The genetics of Tourette syndrome. J Nerv Ment Dis 178:669–679.

Eldridge R, Sweet R, Lake C, Ziegler M, Shapiro A (1977): Gilles de la Tourette syndrome: Clinical, genetic, psychological, and biochemical aspects in 21 selected families. Neurology 27:115–124.

Fernando S (1967): Gilles de la Tourette's syndrome. Br J Psychiatry 113:607–617.

Frankel M, Cummings J, Robertson M, Trimble M, Hill M, Benson F (1986): Obsessions and compulsions in Gilles de la Tourette's syndrome. Neurology 36:378–382.

Gilles de la Tourette (1982): Gilles de la Tourette on Tourette syndrome. In Friedhoff A, Chase T (eds): "Gilles de la Tourette Syndrome (Advances in Neurology)." New York: Raven Press, pp. 1–16.

Green R, Pitman R (1986): Tourette syndrome and obsessive-compulsive disorder. In Jenike M, Baer L, Minichiello W (eds): "Obsessive Compulsive Disorders: Theory and Management." Littleton, MA: PSG Publishing Company.

Jagger J, Prusoff B, Cohen D, Kidd K, Carbonari C, John K (1982): The epidemiology of Tourette's syndrome: A pilot study. Schizophr Bull 8:267–278.

Karno M, Golding J, Sorenson S, Burnam A (1988): The epidemiology of obsessive-compulsive disorder in five U.S. communities. Arch Gen Psychiatry 45:1094–1099.

Kidd K, Pauls D (1982): Genetic hypotheses for Tourette syndrome. In Friedhoff A, Chase T (eds): "Gilles de la Tourette Syndrome (Advances in Neurology)." New York: Raven Press, pp. 243–249.

Kidd K, Prusoff B, Cohen D (1980): Familial pattern of Gilles de la Tourette syndrome. Arch Gen Psychiatry 37:1336–1339.

Kurlan R, Lichter D, Hewitt D (1989) Sensory tics in Tourette's syndrome. Neurology 39:731–734.

Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry 150:98–102.

Lin D (1990): MULCOX: A computer program for the Cox regression analysis of multiple failure time variables. Comput Methods Programs Biomed 32:125–135.

Lin D, Wei L (1989): The robust inference for the Cox proportional hazards model. J Am Statist Assoc 84:1074–1078.

Morphew J, Sim M (1969): Gilles de la Tourette's syndrome. A clinical and psychopathological study. Br J Med Psychol 42:293–301.

Nee L, Caine E, Polinski R, Eldridge R, Ebert M (1980): Gilles de la Tourette syndrome: A clinical and family study of 50 cases. Ann Neurol 7:41–49.

Pauls DL (1992): Issues in genetic studies of Tourette syndrome: Phenotypic spectrum and genetic model parameters. In Chase TN, *Friedhoff AJ*, Cohen DJ (eds): "Gilles de la Tourette Syndrome Second Edition (Advances in Neurology)." New York: Raven Press, pp. 151–157.

Pauls D, Hurst C (1981): "Schedule for Tourette and Other Behavioral Syndromes." New Haven, CT: Child Study Center, Yale University School of Medicine.

Pauls D, Leckman J (1986): The inheritance of Gilles de la Tourette syndrome and associated behaviors: Evidence for autosomal dominant transmission. N Engl J Med 315:993–996.

Pauls D, Cohen D, Heimbuch R, Detlor J, Kidd K (1981): Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics. Arch Gen Psychiatry 38:1091–1093.

Pauls D, Kruger S, Leckman J, Cohen D, Kidd K (1984): The risk of Tourette's syndrome and chronic multiple tics among relatives of Tourette's syndrome patients obtained by direct interview. J Am Acad Child Adolesc Psychiatry 2:134–137.

Pauls D, Towbin K, Leckman J, Zahner G, Cohen D (1986): Gilles de la Tourette's syndrome and obsessive-compulsive disorder. Evidence supporting a genetic relationship. Arch Gen Psychiatry 43:1180–1182.

Pauls D, Pakstis A, Kurlan R, Kidd K, Leckman J, Cohen D, Kidd J, Como P, Sparkes R (1990): Segregation and linkage analysis of Tourette's syndrome and related disorders. J Am Acad Child Adolesc Psychiatry 29:195–203.

Pauls D, Raymond C, Stevenson J, Leckman J (1991): A family study of Gilles de la Tourette's syndrome. Am J Hum Genet 48:154–163.

Pauls DL, Alsobrook JP, Goodman W, Rasmussen S, Leckman JF (1995): A family study of obsessive-compulsive disorder. Am J Psychiatry 152:76–84.

Pitman R, Green R, Jenike M, Mesulam M (1987): Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. Am J Psychiatry 144:1166–1171.

Price R, Pauls D, Caine E (1984): Pedigree and segregation analysis of clinically defined subgroups of Tourette syndrome. Am J Hum Genet [Suppl] 36:178 (abstract).

Puig-Antich J, Orvaschel H, Tabrizi M, Chambers W (1980): "The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (Kiddie-SADS-E)." New York and New Haven: New York State Psychiatric Institute and Yale University School of Medicine.

Risch N (1994): Mapping genes for psychiatric disorders. In Gerson ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, pp 47–61.

Robertson M (1989): The Gilles de la Tourette syndrome: The current status. Br Psychiatry 154:147–169.

Robins L, Helzer J, Croughman J, Williams J, Spitzer R (1980): "The National Institute of Mental Health Diagnostic Interview Schedule, Version 3 (ADM-42-12-79)." Washington, DC: U.S. Government Printing Office.

Santangelo SL (1992): A genetic epidemiologic investigation of Tourette syndrome and its association with obsessive-compulsive disorder. Unpublished doctoral dissertation, Harvard School of Public Health, Boston, MA.

Santangelo SL, Pauls DL, Tsuang MT, Lavori PW, Faraone SV, Goldstein JM (1993): A paradigm for modeling familial risk for Tourette spectrum disorders: Cox regression analysis of multiple failure time variables. Am J Hum Genet [Suppl] 53:855.

Santangelo SL, Pauls DL, Goldstein JM, Faraone SV, Tsuang MT, Leckman JF (1994): Tourette syndrome: What are the influences of gender and co-morbid OCD? J Am Acad Child Adolesc Psychiatry 33:795–804.

SAS Institute, Inc. (1990): "SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2." Cary, NC: SAS Institute, Inc., pp. 1027–1069.

Shapiro A, Shapiro E, Brunn R, Sweet R (1978): "Gilles de la Tourette Syndrome." New York: Raven Press.

Singer H, Walkup J (1991): Tourette syndrome and other tic disorders. Diagnosis, pathophysiology, and treatment. Medicine (Baltimore) 70:15–31.

Walkup J, Leckman J, Price R, Harden M, Ort S, Cohen D (1988): The relationship between Tourette syndrome and obsessive compulsive disorder: A twin study. Psychopharmacol Bull 24:375–379.

Wei L, Lin D, Weissfeld L (1989): Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Statist Assoc 84:1065–1073.

Yaryura-Tobias J, Neziroglu F, Howard S, Fuller B (1981): Clinical aspects of Gilles de la Tourette syndrome. Orthomolec Psychiatry 10:263–268.